Management of Depression Induced by Interferon Hepatitis Therapies

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ABSTRACT

Objective: Treatment with interferon therapy for hepatitis can induce depression and/or recurrence of affective illness, which could result in cessation of interferon treatment. This article reviews treatment for interferon-induced depression, including antidepressant drugs that may diminish associated symptoms.

Data Sources: English-language literature with no date restrictions on the treatment of interferon-induced depression was reviewed via PubMed and MEDLINE using the key words *hepatitis*, *interferon*, *hepatitis C*, *interferon-induced depression*, *pharmacotherapy of interferon-induced depression*, and *depression prevention*. Fourteen of the most pertinent references are cited.

Data Extraction: Escitalopram is the most prominently noted pharmaceutical prescribed for treating mood symptoms in hepatitis patients with interferon-induced depression. Other antidepressant medicines may have utility as well.

Results: Antidepressant drugs can be efficacious in diminishing mood disorders during hepatitis therapies. It remains controversial as to whether antidepressant medications can provide prophylaxis against newly developing interferon-induced depressions in individuals with no past history of a mood disorder.

Conclusions: Antidepressant medicines can be effective at improving mood in patients undergoing interferon treatment for hepatitis.

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Infectious hepatitis is an inflammatory illness of the liver occurring in nearly 4 million Americans.[1] Hepatitis results in approximately 12,000 deaths per year in the United States and is the leading etiology for hepatocellular carcinoma. In chronic cases, hepatitis C is the most common variant of this disease.

The primary pharmacotherapy for hepatitis C is interferon in combination with ribavirin.[2] Interferon works by inhibiting viral replication and activating various immune system cells. Depression is a prominent side effect of interferon therapy. Interferon therapy can induce moderate degrees of depression in up to 70% of patients[1]; up to 40% of patients become severely depressed.[3] Antidepressant drug administration might mitigate this potential medication side effect.[3]

INTERFERON AND MOOD

Interferon may yield depressive symptoms by lowering brain serotonin levels, altering cytokine IL-6 and IL-8 concentrations, and increasing cortisol and adrenocorticotropic hormone concentrations.[4] Depression related to interferon can be severe and occurs especially in the first 3 months of therapy.[4] Risk factors for patients include high-dosage or long-duration interferon therapy and previous history of affective illness. Symptoms include sadness, anhedonia, anorexia, insomnia, and suicidal ideation. Beyond these, other negative consequences resulting from interferon administration include fatigue, irritability, and muscle discomfort. Attempts at suicide are reported in 2% of such patients.[5] The main reason reported for discontinuing or lowering the dose of interferon is significant degrees of depression.[6] Lower doses or discontinuation may diminish the severity of the affective discomfort but can result in the hepatitis treatment being less effective.

This article reviews treatment for interferon-induced depression in patients with hepatitis.

METHOD

English-language literature with no date restrictions on the treatment of interferon-induced depression was reviewed via PubMed and MEDLINE using the key words *hepatitis*, *interferon*, *hepatitis C*, *interferon-induced depression*, *pharmacotherapy of interferon-induced depression*, and *depression prevention*. Fourteen of the most pertinent references are cited.

LITERATURE REVIEW

Escitalopram

A randomized, double-blind study documented that, in subjects who experienced interferon-induced depression, escitalopram reduced the incidence from 19% to 8%, with a confidence interval of 5–15 and a P value of .031.[3] Patients with a past depressive history were excluded. The Mini-International Neuropsychiatric Interview was used to classify preexisting psychiatric illness, and a Montgomery-Asberg Depression Rating Scale score ≥ 13 was used to diagnose depression. Mental health and social function improved more in the escitalopram group compared to those who received placebo; no suicide attempts were reported. Escitalopram therapy did not interfere with response to antiviral therapy and was safe and well tolerated.[3]

Another randomized, double-blind clinical trial revealed efficacy with escitalopram in preventing depression in subjects receiving interferon for

Clinical Points

- For optimal results, antidepressant pharmacotherapy should start 3 months before initiating interferon therapy.
- Most of the antidepressant drugs are effective in treating affective disorders; however, limited efficacy has been reported in the prevention of interferon-induced depression.

treatment of hepatitis C.[7] The Montgomery-Asberg Depression Rating Scale, Brief Anxiety Scale, and Mini-International Neuropsychiatric Interview were utilized to diagnose affective illness. Depression occurred in 13% of those in the escitalopram group compared to 36% of individuals taking placebo, with a *P* value of .015. Additional research on escitalopram and interferon included subjects with a previous history of psychiatric symptoms or depression in remission.[5] In this investigation,[5] 90% of the interferon-treated patients who were also given escitalopram never developed depressive symptoms.

An open-label study with escitalopram in hepatitis C patients receiving interferon evidenced statistically significant improvement in depression.[8] The 17-item Hamilton Depression Rating Scale and Clinical Global Impressions–Severity of Illness scale were used to diagnose depression. The Hamilton Depression Rating Scale score diminished significantly after antidepressant therapy (*P* value of .0001). Substantial improvements in quality-of-life measures and liver function test results were documented.[8]

Citalopram

A prospective, open-label study of subjects undergoing treatment with interferon and ribavirin examined the efficacy of citalopram in managing interferon-induced depression.[9] There was an 85% mood improvement response rate with citalopram pharmacotherapy.[9] The effectiveness of citalopram is equivalent to escitalopram, but citalopram remains questionable with regard to prophylaxis value.[9]

Paroxetine

Two randomized studies revealed that paroxetine did not prevent interferon-induced depression, but it can diminish severity.[10,11] Generalizability was compromised by a small sample size.[10,11]

TREATMENT OPTIONS

There is evidence for most other antidepressant medications to treat interferon-induced depression, but less support for them as prophylactic agents.[12] Selection of the specific pharmaceutical is based on routine clinical criteria, such as hepatotoxicity risk or side effect profile.

There is a significant chance of depression relapse following successful interferon therapies.[13] Antidepressant medication may be indicated at such times. For people who experience depression during a course of interferon, antidepressant drugs should be prescribed for at least 3 to 6 months following the completion of interferon treatment.[13]

Neurovegetative dysfunctions of anorexia, fatigue, or pain can also be complications of interferon hepatitis treatment. These presentations reportedly respond better to antidepressant medicines that augment norepinephrine and/or dopamine than to selective serotonin reuptake inhibitors (SSRIs).[12] Bupropion might be one medication to consider, but some antidepressant options have hepatotoxicity or bone marrow–suppressing potentials that are a confounding factor.[5] Psychostimulants, such as methylphenidate or modafinil, can have utility in counteracting fatigue related to interferon.

PREVENTION

Escitalopram may be effective at preventing depression during interferon therapies, especially if prescribed for the entire 24-week course of interferon exposure.[7] Depression appeared during the first 3 months of interferon administration, and escitalopram provided prophylaxis during that period. Escitalopram is frequently prescribed to treat affective illness. It can also be effective in diminishing interferon-induced depression.[3] In one study,[8] escitalopram was chosen due to its linear pharmacokinetics with negligible cytochrome P450 enzyme action, an advantageous drug interaction profile, and a low hepatotoxicity risk. For optimal results, antidepressant pharmacotherapy should start 3 months before initiating interferon therapy.

In spite of several favorable reviews, some reports[14] do not support the use of escitalopram in prophylaxis against interferon-induced depression. Side effect and drug interaction concerns are cited. Potential adverse effects include nausea, diarrhea, sexual dysfunction, weight gain, and drowsiness.[15] Gastrointestinal bleeding and retinopathies increase in incidence among people with hepatitis C who receive SSRIs.[5] In addition, approximately 60% of patients never experience depression during hepatitis therapies.[6] Thus, they may never have required intervention to improve mood.

CONCLUSION

In hepatitis C patients with a history of depression, escitalopram is effective in preventing the onset or treating the presence of depression induced by interferon therapy. It remains unclear as to whether the same applies to patients without a past history of affective illness.

Efficacy of other antidepressant drugs remains less clear. While such medications are helpful in treating mood disorders, their prophylactic use against the emergence of interferon-induced depression is not substantiated.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), escitalopram (Lexapro and others), methylphenidate (Focalin, Daytrana, and others), modafinil (Provigil), paroxetine (Paxil, Pexeva, and others), ribavirin (Rebetol, ribasphere, and others).

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REFERENCES

1. Viral Hepatitis Statistics and Surveillance. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/hepatitis/statistics/index.htm. Updated June 22, 2012. Accessed October 24, 2012.
2. Interferon. MedicineNet Web site. http://www.medicinenet.com/interferon/article.htm. Updated March 30, 2010. Accessed October 25, 2012.
3. Schaefer M, Sarkar R, Knop V, et al. Escitalopram for the prevention of peginterferon-α2a–associated depression in hepatitis C virus–infected patients without previous psychiatric disease: a randomized trial. *Ann Intern Med*. 2012;157(2):94–103.
4. Crone CC, Gabriel GM, Wise TN. Managing the neuropsychiatric side effects of interferon-based therapy for hepatitis C. *Cleve Clin J Med*. 2004;71(suppl 3):S27–S32.
5. Gleason OC, Fucci JC, Yates WR, et al. Preventing relapse of major depression during interferon-alpha therapy for hepatitis C: a pilot study. *Dig Dis Sci*. 2007;52(10):2557–2563.
6. Asnis GM, De La Garza R 2nd. Interferon-induced depression: strategies in treatment. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29(5):808–818.
7. de Knegt RJ, Bezemer G, Van Gool AR, et al. Randomised clinical trial: escitalopram for the prevention of psychiatric adverse events during treatment with peginterferon-alfa-2a and ribavirin for chronic hepatitis C. *Aliment Pharmacol Ther*. 2011;34(11–12):1306–1317.
8. Gleason OC, Yates WR, Philipsen MA. Major depressive disorder in hepatitis C: an open-label trial of escitalopram. *Prim Care Companion J Clin Psychiatry*. 2005;7(5):225–230.
9. Alberti A. What are the comorbidities influencing the management of patients and the response to therapy in chronic hepatitis C? *Liver Int*. 2009;29(suppl 1):15–18.
10. Morasco BJ, Rifai MA, Loftis JM, et al. A randomized trial of paroxetine to prevent interferon-alpha–induced depression in patients with hepatitis C. *J Affect Disord*. 2007;103(1–3):83–90.
11. Raison CL, Woolwine BJ, Demetrashvili MF, et al. Paroxetine for prevention of depressive symptoms induced by interferon-alpha and ribavirin for hepatitis C. *Aliment Pharmacol Ther*. 2007;25(10):1163–1174.
12. Raison CL, Demetrashvili M, Capuron L, et al. Neuropsychiatric adverse effects of interferon-α: recognition and management. *CNS Drugs*. 2005;19(2):105–123.
13. Lotrich F. Inflammation, interferon-alpha and depression. *Psychiatr Ann*. 2012;42(9):317–321.
14. Diez-Quevedo C, Masnou H, Planas R, et al. Prophylactic treatment with escitalopram of pegylated interferon alfa-2a–induced depression in hepatitis C: a 12-week, randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2011;72(4):522–528.
15. Selective serotonin reuptake inhibitors. Mayo Clinic Web site. http://www.mayoclinic.com/health/ssris/MH00066. Updated December 9, 2010. Accessed October 24, 2012.